

## Perspectives in Practice

Vitamin D and Autoimmune Disease—  
Implications for Practice from the Multiple  
Sclerosis Literature

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## ABSTRACT

Recent studies and commentaries link vitamin D with several autoimmune diseases, including multiple sclerosis (MS). Adequate vitamin D intake reduces inflammatory cytokines through control of gene expression, thus inadequate vitamin D intake is suggested as a mechanism that could contribute to inflammation and, consequently, development of MS. Poor vitamin D status has been associated with increased risk for development of MS, and patients with MS may suffer consequences of vitamin D deficiency, such as bone loss. Animal studies and very limited human data suggest possible benefit from vitamin D supplementation in patients with MS. Based on the current state of research, a key principle for practicing dietetics professionals is to include vitamin D status in nutritional assessment. For those at risk for poor vitamin D status, intake can be enhanced by food-based advice and, when indicated, vitamin D supplementation.

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As translators of nutrition science, dietetics professionals should be attuned to the latest insights into interaction of genes and the nutritional environment. Current research points to a role of vitamin D in regulation of gene expression and production of cytokines that could thwart autoimmune diseases. Dietetics professionals should consider vitamin D carefully in nutritional assessment and when advising the public. This article focuses on the link between vitamin D and multiple sclerosis (MS) and presents implications for dietetics practice.

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## VITAMIN D METABOLISM

Vitamin D status is influenced by both exposure to sunlight and vitamin D content of the diet (Table 1) (1,2). Skin sebaceous glands produce 7-dehydrocholesterol, which upon ultraviolet (UV) B irradiation becomes cholecalciferol or vitamin D-3 and is carried in the blood by vitamin D binding protein. Dietary vitamin D is provided primarily by vitamin D-fortified milk and fish, as shown in Table 1. As a fat-soluble vitamin, dietary vitamin D is absorbed in the small intestine and carried in the blood by chylomicrons. Whether its origin was diet or UV synthesis, vitamin D is first transported to the liver, where it is hydroxylated, and then to the kidney, where a second hydroxylation results in the active form, 1,25-dihydroxyvitamin D, also known as calcitriol (3). Formation of the active molecule is inhibited by several conditions: high plasma concentrations of calcitriol, calcium, and phosphorus; absence of parathyroid hormone; and kidney disease (1,4). Under normal conditions, only small amounts of the dihydroxy compound are found in circulation, thus vitamin D status is typically assessed using serum 25-hydroxyvitamin D levels (5). The Dietary Reference Intakes describes the normal range as 8 ng/mL (20 nmol/L) to 15 ng/mL (37.5 nmol/L) (5).

At a cellular level, 1,25-dihydroxyvitamin D binds to a plasma membrane receptor, resulting in second messenger signaling within the cell. It also acts as a fat-soluble hormone. Its hormone action occurs when 1,25-dihydroxyvitamin D complexes in the cytoplasm with the vitamin D receptor and the retinoid X receptor and is transported through the cytoplasm and across the nuclear membrane. The hormone-receptor complex then binds to DNA, regulating gene expression for different proteins, such as osteocalcin, which fosters bone formation, and cytokines that modulate the immune system (6-10). By regulating production of cytokines, vitamin D can affect inflammation, a hallmark of active autoimmune disease. For instance, by regulating transcription of interleukin-12, 1,25-dihydroxyvitamin D can inhibit secretion of interferon- $\gamma$ , reducing an inflammatory response (6,11). The role of calcitriol in regulation of gene expression also affects cellular differentiation and proliferation; preliminary evidence suggests a role in reducing malignancy (12).

## VITAMIN D SOURCES AND RECOMMENDED INTAKE

According to the current Dietary Reference Intakes, the Adequate Intake (AI) for vitamin D is between 5  $\mu$ g and 15  $\mu$ g per day (depending on age, sex, pregnancy, and lactation), assuming insufficient sun exposure (5). As 1  $\mu$ g equals 40 IU of vitamin D, intake goals are 5  $\mu$ g or 200

Source	Per Common Serving Size	
	IU	$\mu\text{g}^b$
<b>Dairy foods</b>		
Milk, whole, fortified, 1 cup	99	2.5
Edam cheese, 1 oz	10	0.3
Parmesan cheese (hard), 1 oz	8	0.2
Swiss cheese, 1 oz	12	0.3
<b>Eggs and soy</b>		
Egg, whole fresh chicken, 1 large	17	0.4
Soy milk, fortified, 1 cup	100	2.5
<b>Seafood</b>		
Fish oil, cod liver, 1 Tbsp	1,360	34
Mackerel, Atlantic, canned in oil, 3 oz	205	5.1
Herring, pickled, 3 oz	612	15.3
Salmon, canned pink, 3 oz	562	14.0
Sardines, canned in oil, drained solids with bone	77	1.9
Oysters, 3 oz	320	8.0
Shrimp, 3 oz	137	3.4
<b>Meat</b>		
Braunschweiger, 1 oz	12	0.3
Olive loaf, 1 oz	12	0.3
Salami, Cotto beef, 1 oz	14	0.3
<b>Vegetables</b>		
Mushrooms, shiitake, dried, 4 mushrooms	249	6.2

<sup>a</sup>Data from: US Department of Agriculture. National Nutrient Database for Standard Reference, version 17. Available at: <http://www.ars.usda.gov/fnic/foodcomp/search/index.html>. Accessed February 28, 2005. Provisional table on the vitamin D content of foods. Available at: [http://www.nal.usda.gov/fnic/foodcomp/Data/Other/vit\\_d99.pdf](http://www.nal.usda.gov/fnic/foodcomp/Data/Other/vit_d99.pdf). Accessed February 28, 2005.

<sup>b</sup>Micrograms, 40 IU=1  $\mu\text{g}$ .

IU for adults, 10  $\mu\text{g}$  or 400 IU for adults 51 to 70, and 15  $\mu\text{g}$  or 600 IU for those over 70 years of age. In contrast to the AI, information on the nutrition label is based on the recommended daily intake of 400 IU per day. Some researchers suggest increasing the daily intake from 5 to 15  $\mu\text{g}$  per day up to 20 or 25  $\mu\text{g}$  per day to reach serum levels of 25-hydroxyvitamin D of 28 ng/mL (70 nmol/L) (6,13,14). Analysis of data from the Third National Health and Nutrition Examination Survey 1988-1994 and from the Continuing Survey of Food Intakes by Individuals (CSFII 1994-1996, 1998) reveals that mean vitamin D intake for US men reaches the AI of 5  $\mu\text{g}$  per day, but the average intake for US women reaches the AI only when supplements are included (15).

#### VITAMIN D INTAKE AND RISK OF MS

MS is an autoimmune disease in which the body makes autoantibodies against the myelin sheaths surrounding neuron axons, destroying the nerve insulation and thus nerve transmission. Emerging evidence for the role of vitamin D in MS has been reviewed recently (16,17). Interest in vitamin D and MS originated from identification of a negative correlation between exposure to sunlight and preva-

lence of MS. At the equator, where one receives the most UV irradiation over time, MS occurrence is near 0%. The prevalence significantly increases to 50 cases per million people at 45° north or south of the equator (halfway to the North Pole from the equator). In the United States, this falls in the vicinity of Wisconsin or Michigan. The body synthesizes vitamin D from sunlight in northern latitudes at a lesser rate than it does in latitudes near the equator. Thus, the prevalence of MS parallels the reduction in sunlight exposure and potential for vitamin D production (18,19).

Epidemiological data also associate poor dietary vitamin D with incidence of MS. Food frequency questionnaires (FFQs), administered every 4 years to almost 200,000 women in the Nurses' Health Study (followed for 20 years) and the Nurses' Health Study II (followed for 10 years), were assessed for vitamin D intake from food and supplements. Because amounts of vitamin D in supplements were not available, daily supplementation with 400 IU was assumed if supplements were reported. Plasma levels of 25-hydroxyvitamin D were also obtained. Those women in the highest quintile of vitamin D intake (599 to 714 IU/day) had a mean plasma 25-hydroxyvitamin D concentration of 30 ng/mL (75 nmol/L), while those in the lowest quintile (87 to 135 IU/day) had a mean 25-hydroxyvitamin D concentration of 22 ng/mL (55 nmol/L). Women in the highest quintile for intake of vitamin D were more likely to take multivitamin-mineral supplements and less likely to smoke than women in the lowest quintile, confounding results to some extent, because other nutrients may contribute to disease status. MS was reported by 173 participants post baseline. Based on combined diet and supplement intake, a 40% reduced risk of MS was found among women in the highest quintile of vitamin D intake compared with those in the lowest quintile. When analyzed separately, vitamin D supplementation, but not vitamin D from food alone, showed a considerable relationship with MS incidence (20). This lack of association from diet alone may be a result of the difficulty in accurately capturing dietary intake of vitamin D by use of FFQ or perhaps because of a smaller range of vitamin D intake based on diet alone. Although validity of the FFQ was supported by correlation of FFQ data with analysis of food records in a subgroup of participants, as well as lower plasma 25-hydroxyvitamin D levels among those in the lowest quintile of vitamin D intake, others have raised questions regarding this study's analyses (21).

Another observation of vitamin D intake and MS comes from a 1952 study of regions in Norway, where vitamin D synthesis from UV irradiation is limited. Intake was based on measurement of food entering homes in selected coastal and inland locations. Among the residents in lower economic coastal locations, where intake of foods rich in vitamin D was high (cod liver oil and herring), few cases of MS occurred. Incidence of MS increased inland, where farming and dairy provide good income, and thus diets were high in dairy fats and low in good sources of vitamin D (18,22). An MS incidence ratio of 4.1:1.2 was determined when comparing inland to coastal regions.

#### VITAMIN D IN MS PATIENTS

##### Vitamin D Status and Bone Loss in MS

Although vitamin D has been associated with development of MS, once a diagnosis of MS has been established, vitamin

D status continues to be of concern. Increased prevalence of clinical vitamin D deficiency and decreased bone mineral density have been reported in a cross-sectional study of vitamin D status in MS. The majority (80%) of patients in a New York group of 80 women with MS had dietary vitamin D intake below the recommended amount, with about one fourth of the women having a serum 25-hydroxyvitamin D level below 10 ng/mL (25 nmol/L) (23). Among men with MS, 37.5% had low serum 25-hydroxyvitamin D (24). Dual x-ray absorptiometry scans in New York (23,24) and Turkey (25) reported lower bone density among MS patients compared with control subjects. Among the New York males with MS, 37.5% had osteoporosis (24).

Bone health of MS patients can be especially compromised by glucocorticoids, frequently a part of the treatment regimen. One study of 71 female patients with age-matched controls considered glucocorticoid use, immobilization, vitamin D deficiency, and muscle atrophy in relation to bone health. Compared to controls, nonambulatory patients with MS had significantly decreased total bone mineral content ( $-0.6 \pm 0.1$  [mean  $\pm$  standard deviation];  $P < 0.01$ ) and fat-free mass ( $-0.6 \pm 0.1$  [mean  $\pm$  standard deviation];  $P < 0.01$ ). Ambulatory MS patients fared better, but still had reduced bone mass because of decreased physical activity and loss of muscle mass from glucocorticoid use (26). In another study, approximately 50 MS patients with matched controls were followed for 2 years for vitamin D status and the occurrence of fractures and bone loss. MS patients had significantly higher occurrence of fractures than controls (22% vs 2%) and greater bone loss in the femoral head (3% to 6% per year vs 0.5% to 0.8% for women, 7.3% per year vs 1.6% for men). Spine bone loss was more rapid among the MS patients with lower ( $< 20$  ng/mL [ $< 50$  nmol/L]) 25-hydroxyvitamin D levels. The authors conclude that patients might reduce the rate of bone loss and fractures with adequate vitamin D (27).

### Cytokine Profiles of MS Patients

In addition to bone abnormalities, MS patients typically display immune parameters consistent with limited vitamin D activity available to influence gene expression of cytokines. Cytokines are proteins used as a source of communication between immune system cells and cells of other organ systems. Most importantly, cytokines can considerably enhance or attenuate an inflammatory response. Cytokines are typically out of balance in patients with autoimmune disease, with proinflammatory cytokines high and anti-inflammatory cytokines low. Thus, compared with a healthy person, MS patients have increased levels of inflammatory cytokines (eg, interleukin-2, tumor necrosis factor- $\alpha$ , and interferon- $\gamma$ ), as well as lower levels of some anti-inflammatory cytokines (28-31). This imbalance of cytokines in patients with autoimmune disease manifests in disease symptoms related to inflammation. By enhancing the vitamin D status of MS patients, it may be possible for vitamin D to affect the gene expression of these cytokines and alleviate disease symptoms. However, disease manifestation may not only be related to poor vitamin D intake and exposure to sunlight. Among genetic variation, changes in the gene for the vitamin D receptor may reduce the action of vitamin D in gene regulation. Polymorphisms in certain genes, such as the gene for the vitamin D receptor, have

been associated with greater likelihood of MS (32-35). For example, in Japan when 77 MS patients were compared with 95 controls, the MS patients had a significantly higher incidence ( $P = 0.007$ ) of an *ApaI* restriction fragment length polymorphism in the vitamin D receptor gene, suggesting an increased susceptibility to MS (33).

Currently, MS and other inflammatory conditions are treated with corticosteroids, resulting in substantial side effects, such as weight gain, development of diabetes, cataracts, and osteoporosis. The fact that vitamin D has the potential to ease disease inflammation is noteworthy, given these undesirable effects. It is interesting to note that vitamin D and glucocorticoids both quiet inflammation by modulating the immune system, but in quite different manners (36). Proinflammatory cytokines are major targets of glucocorticoids, while major histocompatibility proteins and costimulatory ligands are minor targets, and withdrawal of glucocorticoids may cause a rebound in inflammation. High doses of glucocorticoids are often necessary, thereby contributing to undesirable side effects. On the other hand, hormone action of vitamin D means it is needed in very small amounts. Production of the active form of vitamin D is tightly regulated by the body, given sufficient substrate and proper amounts of calcium.

### VITAMIN D SUPPLEMENTATION IN MURINE MODEL

Given increased incidence of poor vitamin D status among MS patients, could vitamin D supplementation be beneficial? First, two animal studies will be considered. Experimental autoimmune encephalomyelitis (EAE) has been viewed as a mouse model of human MS. EAE is a disease of the central nervous system, mediated by CD4<sup>+</sup> lymphocytes, resulting in an imbalance in cytokines. Symptoms include demyelination and paralysis. These MS-like symptoms can be induced in mice secondary to immunization with myelin basic protein. If vitamin D is provided shortly before induction, disease manifestation is prevented. In addition, if vitamin D is provided postinduction, when disease symptoms have developed, administration of vitamin D reverses disease symptoms. Finally, if vitamin D supplementation is discontinued, disease symptoms will reappear (37).

A second animal study suggests apoptosis of cells secreting proinflammatory cytokines as a possible mechanism of MS symptom alleviation with vitamin D. Researchers induced EAE in mice and then hybridized spinal cord RNA onto DNA microarrays to determine temporal gene expression. Mice that were administered vitamin D had a significantly increased expression of proapoptotic genes such as calpain-2 ( $P < 0.014$ ) and caspase 8-associated protein ( $P = 0.040$ ). In addition, fragments of the nucleus were present, contributing to evidence of apoptosis (38).

One reviewer considers results from animal studies as encouraging, as vitamin D was shown to regulate several different immune system cells in rodents (16). However, another reviewer is skeptical of use of the EAE mouse model to parallel human MS, citing a study demonstrating that the diseases have differing histologies, and the fact that the EAE studies do not explain the geographic distribution and early life migration related to disease occurrence (17).

### Findings

- Limited epidemiological data suggest a link between low vitamin D status and prevalence of multiple sclerosis (MS). This includes variations in vitamin D status due to sunlight exposure, as well as use of vitamin D supplements and routine intake of vitamin D-rich fish.
- Patients with MS have lower serum 25-hydroxyvitamin D than control subjects. These lower levels are borne out in decreased bone mineral status, as well as a cytokine milieu consistent with less than optimum vitamin D availability.
- Mouse models and human studies suggest that vitamin D supplementation may decrease MS disease symptoms.

**Figure 1.** Summary of research related to vitamin D and multiple sclerosis.

### VITAMIN D SUPPLEMENTATION IN MS PATIENTS

In the area of human research, two older reports, although limited, do point in the direction of benefit of nutritional supplementation for MS patients (39,40). A group of 16 MS patients served as their own control for comparison of daily supplementation with cod liver oil that provided 5,000 IU vitamin D and dolomite tablets that provided 16 mg/kg calcium and 10 mg/kg magnesium. Throughout the study, serum 25-hydroxyvitamin D levels ranged from 15 to 80 ng/mL (37.5 to 200 nmol/L). After 1 year, exacerbation of symptoms was reduced by 59%, compared with the previous year without supplementation. However, 6 of 16 subjects dropped out of the study, preventing any viable conclusion from the data (39). In a study aimed at increasing n-3 fatty acids, 16 MS patients received 0.9 g/day of long-chain fatty acids and vitamins, including 10 µg vitamin D. In addition, dietary advice resulted in doubling of fish intake. Symptoms improved in 11 of the 16 patients during supplementation, while they worsened in only one patient. Unfortunately, biochemical parameters of vitamin D status were not assessed (40).

A recent double-blind randomized trial included MS patients with serum 25-hydroxyvitamin D levels below 20 ng/mL (50 nmol/L) (less than half of the optimal range of 40 to 100 ng/mL [100 to 250 nmol/L]). All patients received 800

mg calcium daily for 6 months. Experimental patients (n=17) also received 1,000 IU vitamin D daily, while control patients (n=22) received a placebo. In the experimental patients, serum 25-hydroxyvitamin D improved, but did not reach normal levels; values did not improve in the control subjects. Vitamin D supplementation increased the anti-inflammatory cytokine, transforming growth factor-β1, but other cytokines (interferon-γ, interleukin-2, and interleukin-13) were not changed considerably. Although the results suggest some benefit from vitamin D supplementation, further research with larger numbers of patients is needed (41).

A concern of treatment with vitamin D is that to achieve the immune-modulation benefits, calcitriol must be given in amounts that would produce a serious condition of hypercalcemia in humans. A possible remedy would be to provide less calcium in the diet, as was done in the mice studies. Alternatively, vitamin D analogs could be used to treat MS. Although analogs have been developed that would not raise serum calcium levels, they have not yet been shown effective in humans with MS (42).

The research related to vitamin D and multiple sclerosis is summarized in Figure 1. MS is just one example of autoimmune disease recently linked to vitamin D. The incidence of type 1 diabetes mellitus has been also been associated with vitamin D (43). Type 1 diabetes occurs less frequently among adults who received vitamin D supplementation during infancy (44) and among children born to mothers who consumed a vitamin D-rich diet during pregnancy (45). In addition, vitamin D is being investigated for its role in rheumatoid arthritis and other autoimmune diseases (46,47) and in the development of cancer (12,48).

### CONSIDERATIONS FOR FURTHER RESEARCH

As the nutrition science and medical communities investigate the role of vitamin D in a growing number of chronic diseases, several issues face dietetics professionals. Dietetics researchers should include vitamin D as they consider design and analysis of studies related to such autoimmune diseases as MS and type 1 diabetes mellitus. When considering dietary intake in relation to chronic disease, dietitians should not ignore vitamin D intake from foods (primarily milk and fish), as well as

**Table 2.** Calcium and vitamin D content of selected supplements

Preparation	Manufacturer	Serving size	Calcium (mg)	Vitamin D (IU)
Calcium supplements				
Caltrate	Wyeth, Madison, NY	1 tablet	600	200
Citracal	Mission Pharmaceuticals, San Antonio, TX	2 caplets	630	400
Oscal	GlaxoSmithKline, Pittsburgh, PA	1 tablet	600	200
Viactiv Calcium	McNeil Nutritionals, Ft. Washington, PA	1 chew	500	100
Multivitamin/mineral supplements				
One-A-Day Essential	Bayer, Morristown, NJ	1 tablet	NA <sup>a</sup>	400
Centrum	Wyeth, Madison, NY	1 tablet	162	400
Centrum Silver	Wyeth, Madison, NY	1 tablet	200	400
One-A-Day 50 Plus	Bayer, Morristown, NJ	1 tablet	240	400

<sup>a</sup>NA—not available.

Recommendation	Rationale
Encourage clients to consume dairy products, including lactose-free products, as needed.	Vitamin D intake can be decreased when soft drinks replace milk, a currently popular practice (50). Lactose intolerance may also reduce vitamin D intake from dairy products.
Advise clients to read the label and choose a yogurt (or other dairy product) that includes vitamin D.	Yogurt, a popular way to get calcium, may or may not be produced from vitamin D–fortified milk.
Foster intake of fish by providing tasty recipes and simple instructions on how to cook fish, including how to achieve the correct level of doneness.	Fish is a good source of vitamin D, but some people avoid fish because they do not know how to prepare it healthfully.
For breastfed infants who do not consume at least 500 mL/day of a vitamin D–fortified beverage, supplement vitamin D starting within the first 2 months of life.	Rickets have been reported in a few totally breastfed infants, especially among dark-skinned infants in northern latitudes. The American Academy of Pediatrics (51) recommends vitamin D supplementation.
Encourage darker-skinned people without good sunlight exposure to consume vitamin D–rich foods. Older adults may benefit from a multivitamin/mineral supplement.	Synthesis of vitamin D from sunlight varies with skin qualities. Darker-skinned people and older adults synthesize vitamin D from the sun less efficiently (5,52–54).
Apply sunscreen after 15 minutes of sun exposure to optimize vitamin D production while promoting cancer prevention.	Avoiding sunshine or using sunscreen to prevent skin cancer eliminates vitamin D synthesis activated by sunlight (55). Window glass also blocks ultraviolet B rays that trigger vitamin D synthesis.
Suggest outdoor activities when encouraging regular physical activity for health and weight control.	Today's lifestyle of exercising in the gym, children staying inside while parents are at work, and covered parking and walkways can reduce sun exposure.
Caution individuals not to exceed the upper limit for vitamin D intake (50 µg/day or 2,000 IU for those over the age of 1 year).	Excessive intake could occur with supplement use or extensive use of vitamin D–fortified functional foods. Overexposure to sunlight does not cause hypervitaminosis D.

**Figure 2.** Recommendations for improved vitamin D status in cases of different life habits, food tolerances, ethnicities, and age groups in the United States.

potential for vitamin D synthesis from sunlight exposure. Data due out shortly from the Women's Health Initiative could offer an opportunity to investigate associations of vitamin D intake with diseases such as MS and breast cancer. As other cohort studies are designed, vitamin D can be included as one of the nutrients assessed carefully.

With current interest in n-3 fatty acids and chronic illness, such as cardiovascular disease, distinctions should be made between intake of long-chain fatty acids found in fish and the vitamin D present in fatty fish as they relate to impact on disease. Perhaps the promising results from intake of fish found in the Lyon Heart Study (49) is partly a result of an anti-inflammatory benefit of vitamin D present in the fish, and not just the beneficial n-3 fatty acids. In the Lyon Heart Study, approximately 600 patients with a history of myocardial infarction were randomized to either a Mediterranean-type diet high in fish or a prudent Western-type diet. The high-fish diet resulted in a risk ratio of 0.28 ( $P=0.0001$ ) for death and nonfatal myocardial infarction events. Thus, distinguishing between vitamin D and n-3 fatty acids as two important nutritional contributions of fish may help to explain why reported benefits of fish consumption are not always borne out in trials of fish oil supplements.

## CONCLUSIONS

For the clinical practitioner, assessment of diet should not only consider intake of fruits and vegetables, fiber, and saturated fat to reduce chronic disease, but should also assess sources of vitamin D from foods (primarily milk and fish) and from sunlight exposure. The dietetics professional can be alert to a variety of reasons why individuals may not obtain sufficient daily vitamin D. When individuals do not consume the food sources of vitamin D shown in Table 1, supplements can be used. Table 2 compares the vitamin D content of several popular calcium and multivitamin preparations. In the future, dietetics professionals may also rely on information generated from nutrigenomic data for individuals and adjust their assessment and recommendations accordingly. Recommendations for advice to clients on vitamin D are provided in Figure 2.

When faced with questions from MS patients regarding vitamin D supplementation, the dietetics professional can assess vitamin D intake and encourage intake from foods and supplements to achieve at least the AI of 400 IU or possibly twice that level (13), but should not exceed the tolerable upper limit of 2,000 IU (5). Maintaining good vitamin D status would be encouraged to reduce bone loss. However, the dietetics professional should be careful

not to overstate possible benefit in terms of treatment of the disease itself. Therapeutic use of calcitriol or its analogs is only at early experimental stages.

In conclusion, emerging evidence suggests a link between vitamin D intake and autoimmune diseases like MS. As further research is undertaken, it appears prudent to attend to the vitamin D status of clients and ensure adequate vitamin D intake.

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